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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,279	01/16/2002	James P. Fandl	REG 790A	7032

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,279	FANDL ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,23,45-63,66-84 and 87* is/are pending in the application.

4a) Of the above claim(s) *2,4,6,8,47,49,51,68 and 70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,9-20,23,45,46,48,50,52-63,66,67,69,71-84 and 87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *21 January 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 16 January 2002, which claims benefit of the U.S. Provisional application filed 16 January 2001. The amendments filed 22 September 2003 and 12 February 2004 have been entered. Claims 1-86 were originally filed. Claims 21, 22, 24-44, 64, 65, 85 and 86 were canceled, claims 20, 23, 45, 58, 63, 66, 79, 81 and 84 were amended, and claim 87 was added in the 12 February Paper. Claims 1-20, 23, 45-63, 66-84 and 87 are pending.

Election/Restrictions

Applicant's election of Group I and the linked species wherein the protein of interest is an IgG and the cell surface capture molecule is an Fc receptor in the Paper filed 29 March 2004 is acknowledged. Because applicant did not distinctly and specifically point out errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 4, 6, 8, 47, 49, 51, 68 and 70, directed to non-elected embodiments of the protein of interest and cell surface capture molecule, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 3, 5, 7, 9-20,23, 45, 46, 48, 50, 52-63, 66, 67, 69, 71-84 and 87 are presently under consideration.

Claim Objections

Claims 52 and 87 are objected to because of the following informalities:

Claim 52 is grammatically incorrect. The plural "receptors", "antibodies", etc. does not agree with the singular "antibody binding protein".

Claim 87 contains a typographical error in line 3. Specifically, the claim recites, "culturing those cells detected in (b)", while it is clear from the context and similar language used in claim 23 that the claim should read, "culturing those cells detected in (a')".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7, 9-20,23, 45, 46, 48, 50, 52-63, 66, 67, 69, 71-84 and 87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting and isolating cells that produce a secreted protein of interest wherein:

the protein of interest comprises an antibody Fc domain;

the cell surface capture molecule is an Fc receptor or a surface displayed protein G chimera;

the detection molecule is an antibody specific for the protein of interest or, when the protein of interest is an antibody, an antigen to which the protein of interest binds; and the cell is a mammalian cell,

does not reasonably provide enablement for the method wherein: the protein of interest is any secreted protein; the cell surface capture molecule is any expressed protein; and the detection molecule is any molecule which binds to the protein of interest. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method of detecting and isolating cells that produce a secreted protein by constructing a cell that express both the secreted protein and a cell surface molecule that binds to the secreted protein so that the secreted protein is displayed on the surface of cells that secrete the protein. Cells having the surface displayed protein of interest are then detected by contacting the cells with a second molecule that binds to the protein of interest. The specification provides no particular limitations on the protein of interest, other than that it is secreted; places no particular limitations on the capture molecule, other than that it is expressed on the surface of a cell; and places no particular limitations on the detection molecule or the cell in which the proteins are expressed. Thus, the

claimed method broadly encompasses a method of detecting and isolating a cell expressing any secreted protein by coexpressing any cell surface molecule that binds to the secreted protein in any cell and detecting the surface-displayed protein of interest with any molecule that detects the protein of interest.

State of the prior art and level of predictability in the art: Practicing the instant method requires the formation of a complex comprised of a cell surface attached capture molecule bound to the secreted protein of interest, which is in turn bound to a detection molecule, such that the complex is sufficiently stable to allow for detection and isolation of the cell by methods such as fluorescence activated cell sorting. Elements critical to the function of the claimed method logically include the binding affinity of each of the surface capture molecule and the detection molecule for the protein of interest, and the ability of each molecule to bind to the protein of interest without interfering with the binding of the other molecule.

With regard to the binding affinity of the individual proteins, the art provides no guidance as to what the minimum requirements would be to maintain an intact cell surface complex long enough to allow purification of the cell. It is important to recognize that the binding of the complex constituents would be, in most cases, non-covalent and therefore subject to the law of mass action. Further, the data presented in the working examples shows that practicing the method requires that reassociation of the protein of interest with unbound surface capture molecules be suppressed in order to block the transfer of the secreted protein of interest from expressing cells to non-expressing cells (see Example 1, especially lines 19-22 on page 38). Therefore, the stability of the surface complex as a whole would be dictated by the dissociation rate of the protein of interest from the cell surface capture molecule. As the skilled artisan would

not be able to predict the binding affinity that would enable purification of the expressing cell based on the presence of the cell surface complex, the operability of the claimed invention would have to be determined empirically for each unique surface protein and protein of interest.

Likewise, the art does not provide the skilled artisan with the means to predict which combinations of surface capture molecule and detection molecule would be operable together. Clearly, in order for the method to operate, the binding moieties cannot interfere with one another to the extent that the complex becomes too unstable to allow for purification of the cell. Absent some limitation that would restrict binding of the surface capture molecule and detection molecule to distinct domains of the protein of interest, the skilled artisan would have to resort to trial and error experimentation to identify each operable surface capture molecule-detection molecule combination to be used in the claimed method.

Furthermore, the claimed method broadly encompasses isolating a cell based on the cell surface expression of essentially any protein at the same time as essentially any secreted protein is expressed in the same cell, wherein the cell can be any prokaryotic or eukaryotic cell. However, the art recognizes that obtaining expression of any given protein in any given cell is often unpredictable. For example, Goeddel (1990) *Methods Enzymol.* 185:3-5 teaches, "[i]n general, the expression of each cDNA or gene presents its own peculiar set of problems that must be overcome to achieve high-level expression. The synthesis of foreign proteins is still largely empirical. There is no set of hard-and-fast rules to follow. In fact, a particular protein is almost as likely to be the exception as it is to follow any set of rules" (page 3, paragraph 3). Thus, Goeddel teaches that protein expression in heterologous systems is unpredictable. The Examiner is not

aware of any teachings published after Goeddel to indicate that the present state of the art is generally enabling for expression of any protein in any cell.

Significantly, because many of the proteins encompassed by the surface capture molecule of the claims, including Fc receptor molecules, would be membrane bound, recent developments in the art demonstrate that functional heterologous expression of membrane proteins is particularly problematic because their function is often dependent upon the characteristics of the lipid environment. Opekarová *et al.* (2003) *Biochim. Biophys. Acta* 1610:11-22 teaches, "[a]n important open question has long been, whether membrane proteins are associated with specific lipids and whether they are dependent on these for structural integrity and function. Considerable evidence confirming that this is indeed the case has been published within the last few years" (bridging the left and right columns on page 11). Thus, Opekarová *et al.* teaches that the structural integrity and function of membrane proteins is dependent upon the lipid environment, which differs from one organism to the next (see especially Table 3). However, the art does not provides the means to predict whether, or how a given membrane protein will respond to expression in a given lipid environment. Therefore, the skilled artisan is not able to predict which surface capture molecules could be expressed in any given cell type such that the cell could be used in the claimed method without having to engage in empirical experimentation.

The problem of obtaining functional heterologous expression of surface proteins such that they could be used as cell surface capture molecules in the instant method is particularly acute when the method is practiced with a microbial cell type. With regard to surface display of passenger proteins on microbes, Lee *et al.* (2003) *TRENDS Biotechnol.* 21 :45-52 teaches that a variety of factors can interfere with functional expression in unpredictable ways. For example,

the passenger proteins can influence the translocation process (paragraph bridging the left and right columns on page 46); steric hindrance, incomplete exposure, and unfolded or misfolded structure of expressed protein can interfere with function as well as artifacts induced by cell-envelope changes (paragraph bridging pages 50-51).

Thus, the formation of a complex comprised of a cell surface attached capture molecule bound to a secreted protein of interest, which is in turn bound to a detection molecule, such that the complex is sufficiently stable to allow for detection and isolation of the cell could not readily be predicted for any given cell surface capture molecule and protein of interest expressed in any given cell.

Amount of direction provided by the inventor and existence of working examples: The working examples set forth in the instant application describe expression of two different antibody Fc domain binding proteins (*i.e.*, FcγRI (Examples 1-7) and protein G (Example 8)) as cell surface capture molecules in either CHO cells or a myeloma cell line. The CHO cells expressing either FcγRI or a surface displayed protein G were then used to purify cells expressing chimeric secretory proteins comprising an antibody Fc domain. Although these examples demonstrate operability of the method wherein an Fcγ receptor or protein G chimera are expressed in mammalian cells and used to identify a cell expressing a secreted protein comprising an antibody Fc domain, there is nothing in the disclosure that would enable the skilled artisan to practice the broad scope of the claimed method. Teachings in the specification with regard to practicing the claimed method using a surface capture molecule other than those reduced to practice are general in nature and do not address the unpredictability in the art. The specification provides no specific guidance that would enable the skilled artisan to predict which

protein complexes (*i.e.*, surface capture molecule, protein of interest and detection molecule) would be compatible and sufficiently stable to use in the claimed method. Furthermore, the specification provides no guidance with regard to practicing the claimed invention other than in mammalian cells. Thus, the teachings of the specification fail to address the unpredictable nature of practicing the claimed method over the broad scope of the claims.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to practice the full scope of the claimed invention without having to first engage in undue experimentation. One of ordinary skill would understand that operability of the claimed invention requires the formation of a complex comprised of a cell surface attached capture molecule bound to the secreted protein of interest, which is in turn bound to a detection molecule, such that the complex is sufficiently stable to allow for detection and isolation of the cell. However, neither the art nor the instant disclosure teach how one might distinguish complexes that would be operable in the method from complexes that would be inoperable short of blindly constructing and testing each complex. Furthermore, the teachings in the disclosure do not address the art-recognized unpredictability of obtaining functional protein expression in heterologous systems. Therefore, practicing the claimed invention in microbial systems, even when operability of the protein complex is demonstrated in mammalian cells, would also require undue experimentation.

For these reasons, practicing the claimed invention commensurate with the full scope of the claims would require undue experimentation. Therefore, the claims are rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5, 7, 9-20,23, 45, 46, 48, 50, 52-63, 66, 67, 69, 71-84 and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation in claims 1, 45 and 66 that the cells are isolated "based on the detection molecule". It is unclear what properties of the detection molecule form the basis for the isolation. It would seem, in light of the specification, that isolation would be based on the presence of the detection molecule; however, the method is not so limited and it is unclear exactly what is encompassed by isolating based on the detection molecule.

Claim 45 is additionally indefinite in the recitation of "said cell surface capture molecule" in line 2. There is no antecedent basis for the limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 45, 46, 48, 50, 53,55, 58-60 and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Miltenyi *et al.* (1994) WO 94/09117.

Miltenyi *et al.* teaches a method of detecting and isolating cells that produce a protein of interest comprising: a) detecting a cell that expresses a cell surface capture molecule in high yield; b) transfecting the cell with a nucleic acid that encodes a secreted protein of interest; c) detecting the surface displayed protein of interest with a detection molecule that binds to the protein of interest; and d) isolating cells based on the presence of the detection molecule. The method is described, *inter alia*, in Example 1, beginning on page 29. In particular, part a), which is understood to encompass expression of the surface capture molecule by any means, can be found in the paragraph beginning at line 25 on page 34; parts c) and d) are can be found in the discussion beginning on page 36 and continued through page 39. Further, in the paragraph bridging pages 24-25, Miltenyi *et al.* contemplates the method wherein a nucleic acid encoding the protein of interest is transfected into the cell according to part b). Thus, Miltenyi *et al.* teaches each of the steps recited in the method of claim 45.

The method of Miltenyi *et al.* further comprises each of the elements of claims 46, 48, 50, 53,55, 58-60 and 63. Miltenyi *et al.* teaches the method wherein the protein of interest is an antibody according to claims 46 and 48, and the capture molecule is an antibody binding protein according to claim 50 (see especially Example 1 and the discussion on pages 23 and 24); wherein the antibody binding protein comprises a synthetic membrane anchor according to claims 53 and 55 (*i.e.*, the avidin moiety used in Example 1 to attach the antibody binding protein to the biotinylated cell surface is understood to read on a membrane anchor as described in the first full paragraph on page 12 of the specification); wherein the isolated cell is a hybridoma according to claims 58-60 (see especially pages 23-24); and wherein diffusion of the protein of interest is

reduced by increasing the viscosity of the media according to claim 63 (see especially Figure 7 and the paragraph bridging pages 36-37).

Miltenyi *et al.* teaches each of the limitations of the instant claims; therefore, the claims are anticipated by Miltenyi *et al.*

Conclusion

Claims 1, 3, 5, 7, 9-20, 23, 52, 54, 56, 61, 62, 66, 67, 69, 71-84 and 87 are free of the art. Although Miltenyi *et al.* contemplates modification of cells by introduction of a product capture system (page 24, lines 32-35), which can be construed to read on transfecting a cell with a nucleic acid that encodes a cell surface capture molecule according to the method of independent claims 1 and 66, Miltenyi *et al.* is not enabling for the broad scope for the reasons set forth herein above, and does not contemplate the enabled embodiments of the instant claims. Therefore, Miltenyi *et al.* does not teach or suggest the enabled subject matter of the instant claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

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PRIMARY EXAMINER